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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/637,887	RAJOTTE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1 and 13-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-26 are pending.

Applicant's election of Group V, claims 3-4, 6-11, drawn in part to a polynucleotide encoding a fusion protein comprising a chymase that specifically localizes to a secretory lysosome and a label polypeptide, and a cell transformed with said polynucleotide, as submitted in a communication filed on 4/3/2006 is acknowledged.

Applicant requests rejoinder of claims 5 and 12 in view of the fact that Rat Mast Cell Protease (RMCP) II is a chymase, and the cell line deposited at ATCC having the accession number PTA-4571 produces a fusion protein comprising RMCP II. Arguments have been fully considered and are deemed persuasive. Claims 5 and 12 are hereby rejoined for examination on the merits.

While Applicant has requested rejoinder of claims 5 and 12 as being directed to the elected invention, the election has been treated as an election without traverse in view of the fact that Applicant has not pointed out the supposed errors in the Examiner's determination as to how many inventions are present in the instant application (MPEP § 818.03(a)).

Claims 1, 13-26 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/403,464 filed on 08/14/2002.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 7/9/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

3. The drawings submitted on 8/8/2003 have been reviewed and are accepted by the Examiner.

Claim Objections

4. Claims 3-11 are objected to because they are partially directed to non-elected inventions (Groups I-IV, VI-VI). These claims will be examined to the extent they read upon the elected subject matter (Group V). Appropriate correction is required.

5. Claim 3 is objected to due to the recitation of "carboxypeptidsases". This appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 4 is indefinite in the recitation of "cathepsin G-like protease" as it is unclear whether the term encompasses a protein having (1) a structure like that of a cathepsin G protease but not necessarily that function, or (2) cathepsin G protease activity. For examination purposes, the term will be interpreted as referring to function. Correction is required.

9. Claim 5 is indefinite in the recitation of "wherein the protease is Rat Mast Cell Protease... ..according to GenBank accession No. J02712" for the following reasons. As known in the art, a sequence in a GenBank entry can be modified at any time and still retain its accession number. Thus, the sequence associated with the GenBank accession number recited is potentially variable. It is suggested that if the sequence for the protease recited has been included in the Sequence Listing, the sequence identifier used in the Sequence Listing be recited instead. For examination purposes, no patentable weight will be given to the term "GenBank accession No. J02712". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 2-4, 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-4, 6 are directed to polynucleotides encoding fusion proteins wherein said fusion proteins encompass a genus of (1) polypeptides that localize to a secretory lysosome, or (2) polypeptides that localize to a secretory lysosome wherein said polypeptides are (i) proteases, (ii) tryptases, (iii) human tryptases, (iv) chymases, (v) human chymases, (vi) carboxypeptidases A, (vii) cathepsin D proteases, or (viii) hexosaminidases. Claims 7-11 are directed to cells comprising the genus of polynucleotides of claim 2.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a

description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

There is no structural limitation with regard to the members of the genus of nucleic acids claimed. While the specification in the instant application discloses the structure of a polynucleotide encoding a fusion protein, wherein the fusion protein comprises rat cell mast protease II (RMCP II) and red fluorescent protein (DsRed), it provides no information as to the structural elements required in a nucleic acid encoding any (1) polypeptide that localizes to a secretory lysosome, or (2) any protease, tryptase, human tryptase, chymase, human chymase, carboxypeptidase A, cathepsin D protease, or hexosaminidase that localizes to a secretory lysosome. Also, there is no disclosure of the structural elements required in human tryptases and chymases which are not found in other tryptases or chymases. The specification fails to describe any additional species by any relevant, identifying characteristics or properties other than by functionality.

The claims encompass an extremely large genus of nucleic acids which are structurally unrelated. A sufficient written description of a genus of nucleic acids may be achieved by a recitation of a representative number of nucleic acids defined by their nucleotide sequence or a recitation of structural

features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of nucleic acids recited in the claims, and there is no information as to a correlation between structure and function. Furthermore, while one could argue that the structure of RMCP II or the structures of other proteases/tryptases/chymases/carboxypeptidases A/hexosaminidases/cathepsin D proteases known in the art are representative of the structure of all members of the genus of proteins encoded by the nucleic acids recited, it is noted that the art teaches several examples of how even small variations in structure result in functional variation. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β–ketoacyl synthase into a malonyl decarboxylase and completely eliminates β–ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the recited activities has been provided, one cannot reasonably conclude that the structures disclosed/known in the art are representative of all the nucleic acids recited.

Due to the fact that the specification only discloses a single species of the genus of nucleic acids recited (i.e., polynucleotide encoding a fusion protein comprising RMCP II and DsRed), as well as the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

12. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ a novel cell line. Since the cell line is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed cell line has not been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the cell line. The specification does not disclose a repeatable process to obtain the cell line and it is not apparent if the cell line is readily available to the public. Accordingly, it is deemed that a deposit of this cell line should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited the cell line but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell line has been deposited under the Budapest Treaty and that the cell line will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

b. upon granting of the patent the cell line will be available to the public under the conditions specified in 37 CFR 1.808;

c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

d. the deposit will be replaced if it should ever become unviable.

13. Claims 2-4, 6-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a fusion protein comprising the rat mast cell protease II and a label polypeptide, as well as an isolated host cell comprising said polynucleotide, does not reasonably provide enablement for (1) a polynucleotide encoding a fusion protein, wherein the fusion protein comprises (i) any polypeptide which localizes to a secretory lysosome, or (ii) any protease, any chymase or tryptase, any cathepsin G protease, any carboxypeptidase A, or any hexosaminidase that localizes to a secretory lysosome, (2) an isolated or non-isolated host cell comprising the polynucleotide of (1), or (3) a non-isolated host cell comprising a polynucleotide encoding a fusion protein, wherein the fusion protein comprises the rat mast cell protease II and a label polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 2-4, 6-11 are so broad as to encompass (1) polynucleotides encoding fusion proteins wherein said fusion proteins comprise any (i) polypeptide that localizes to a secretory lysosome, or (ii) protease, tryptase, human tryptase, chymase, human chymase,

carboxypeptidase A, cathepsin D protease, or hexosaminidase which localizes to a secretory lysosome, and (2) isolated and non-isolated cells comprising the polynucleotides of (1). See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. The enablement provided is not commensurate in scope with the claims due to the extremely large number of nucleic acids of unknown structure recited in the claims. In the instant case, the specification enables a polynucleotide encoding a fusion protein, wherein the fusion protein comprises rat mast cell protease II (RMCP II) and a label polypeptide.

With regard to claims 7-11, it is noted that the specification contemplates the polynucleotides of the invention to be used *in vivo* for studying secretory lysosome maturation, biosynthesis, cell differentiation, migration and activation (page 12, lines 25-27), and to be delivered to a subject for therapeutic purposes (page 13, lines 8-12). Therefore, in its the broadest reasonable interpretation, claims 7-11 are directed not only to isolated host cells but also to host cells within a transgenic multicellular organism (i.e., non-isolated). The enablement provided is not commensurate in scope with the claim due to the extremely large number of transgenic multicellular organisms comprising the cells encompassed by the claims which the specification fails to teach how to generate or how to use. In the instant case, the specification enables an isolated host cell comprising a polynucleotide encoding a fusion protein, wherein the fusion protein comprises RMCP II and a label polypeptide.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a polynucleotide encoding a fusion protein wherein the fusion protein comprises RMCP II and DsRed, and a cell line (RBL-2H3 cells) expressing said polynucleotide, as working examples. However, the specification fails to provide any clue as to (1) the structural elements required in any nucleic acid encoding (i) a polypeptide that localizes to a secretory lysosome, or (ii) a protease, a tryptase, a human tryptase, a chymase, a human chymase, a carboxypeptidase A, a cathepsin D protease, or a hexosaminidase that localizes to a secretory lysosome, or (2) which are the structural elements in the proteins disclosed in the specification or the art which are essential for any protein to display the recited

activities. No correlation between structure and the recited activities has been presented. There is no information or guidance as to which are the amino acid residues in RMCP II required in any protein such that it would localize to a secretory lysosome and display all the activities recited (i.e., tryptase, chymase, carboxypeptidase A, etc.). In addition, there is no disclosure of the structural elements found in human tryptases and chymases that localize to secretory lysosomes not found in tryptases/chymases from other organisms.

With regard to claims 7-11, while the specification discloses that the polynucleotides of the invention can be used to transform host cells for recombinant production of the corresponding fusion protein, the specification also discloses that the polynucleotides of the invention can be used for studying secretory lysosome maturation, biosynthesis, cell differentiation, migration and activation *in vivo* as well as for therapeutic purposes. There are no working examples or specific methods disclosed showing a transgenic animal capable of expressing a polynucleotide encoding a fusion protein comprising RMCP II, or any polypeptide which localizes to a secretory lysosome. Also, there are no working examples or specific methods disclosed showing how to deliver the claimed genus of nucleic acids to human tissues such that the claimed nucleic acids can be used for therapeutic purposes.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of the coding region of a polynucleotide encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and all the activities recited such that one of skill in the art can envision the structure of any nucleic acid encoding a polypeptide having the required activities. In addition, the art does not provide any teaching or guidance as to (1) the structural elements in the proteins disclosed in the specification and those known in the art which are required in any protein which localizes to a secretory lysosome, or (2) which elements in a polynucleotide encoding RMCP II are required in any chymase/protease which localizes to a secretory lysosome. It is also noted that neither the

specification nor the art provide the structural elements required in any protease, chymase, tryptase, cathepsin D protease, carboxypeptidase A, or hexosaminidase such that they would localize to a secretory lysosome. Furthermore, while the argument can be made that the genus of proteins required is enabled due to the fact that there are several proteins known in the art which localize to a secretory lysosome, there is no information provided as to the general tolerance of these proteins to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

With regard to transgenic multicellular organisms, the prior art teaches that making genetically modified animals is highly unpredictable. The relevant art has for many years indicated that the unpredictability of generating transgenic animals lies with the site or sites of integration of the transgene into the target genome. Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992) teach that transgenic animals are known to have inherent cellular mechanisms which may alter the pattern of gene expression, such as DNA methylation or deletion from the genome (page 549, right column, third

paragraph). Furthermore, Mullins et al. (Hypertension 22(4):630-633, 1993) teach that integration of a transgene in different species may result in widely different phenotypic responses (page 631, left column, first paragraph, last sentence). Also, Mullins et al. (J. Clin. Invest. 97(7):1557-1560, 1996) teach that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (page 1559, Summary). Wigley et al. (Reprod. Fert. Dev. 6:585-588, 1994) indicate that transgenesis by microinjection has a number of limitations including random integration in the genome and integration of transgenes in multiple copies at one site such that expression level is not proportional to transgene copy number (page 585, Introduction). Cameron (Molecular Biotechnology 7:253-265, 1997) teaches that well-regulated expression of the transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (page 256, left column, last three lines, right column, first three lines). According to Cameron, transgene expression with different transgenic lines produced with the same constructs is unpredictable and expression levels do not correlate with the number of transgene copies integrated, thus indicating the influence of the integration site on the expression pattern (page 256, right column, lines 3-13).

In regard to DNA delivery and expression in human tissues, the art teaches the high unpredictability of delivering DNA to human tissues and achieving the desired expression. For example, Phillips (J. Pharm. Pharmacology 53:1169-1174, 2001) teaches that the major challenges in gene therapy have been delivery of DNA to target cells and duration of expression (Abstract). According to Phillips, the problem regarding gene therapy is twofold in that (1) a system must be design to deliver DNA to a specific target while preventing degradation within the body, and (2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for a determined amount of time (page 1170, left column, lines 7-15). Gardlik et al. (Med. Sci. Monit. 11(4):RA110-121, 2005) teach that (1) while there are a number of methods known for delivery of DNA, there is no clear

ideal delivery system (RA119, last paragraph), and (2) the main problem in gene therapy lies in the secure and efficient delivery of genes into target cells and tissues (RA110, Summary).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all the polynucleotides which would encode proteins that localize to secretory lysosomes. Furthermore, it is not routine in the art to isolate/create any polynucleotide encoding a protein with the activity recited without any knowledge as to the structural features which would correlate with that activity. In the absence of (1) a rational and predictable scheme for modifying any nucleotide in nucleic acids encoding known proteins which localize to secretory lysosomes such that the resulting variant would encode a protein which displays the same activity, and/or (2) a correlation between structure and the recited activities, one of skill in the art would have to test an essentially infinite number of polynucleotides to determine which ones encode proteins having the ability to localize to a secretory lysosome and have the enzymatic activities recited. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Furthermore, given the teachings of the art regarding the differences in expression of a transgene in different species, the limitations regarding the integration and expression of a transgene, the unpredictability of delivering and expressing DNA in human tissues, and in view of the lack of guidance provided by the specification, it would have required undue experimentation to engineer any transgenic multicellular organism comprising the recited cells.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to (a) structural changes and their effect on function, (b) generation of transgenic multicellular organisms, and (c) delivery and expression of DNA in human tissues, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 2, 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Masuda et al. (FEBS Letters 470:61-64, 2000; cited in the IDS).

Masuda et al. teach a GTPase (Rab37) fused to green fluorescent protein which specifically localizes to secretory granules of bone marrow mast cells (Abstract; page 64, Figure 4; page 63, left column, line 28-right column, line 9). Masuda et al. teach an expression vector comprising the polynucleotide encoding the fusion protein (page 62, left column, lines 4-21; Green fluorescent protein (GFP)-Rab37 fusion protein expression) and expression of said vector in bone marrow mast cells (page 63, left column, line 28-right column, line1). As known in the art, the secretory granules of cells derived from the hemopoietic lineage, such as mast cells, are secretory lysosomes (Griffiths, G. M., Trends in Cell Biology (6):329-331, 1996; Abstract).

Claims 2 and 6 are directed in part to a polynucleotide encoding a fusion protein, wherein said fusion protein comprises (1) a polypeptide which localizes to a secretory lysosome, and (2) a fluorescent polypeptide. Claims 7-11 are directed in part to a mast cell comprising a polynucleotide encoding a fusion protein, wherein said fusion protein comprises (1) a polypeptide which localizes to a secretory lysosome, and (2) green fluorescent protein. Thus, the polynucleotide and cells of Masuda et al. anticipate the instant claims as written.

16. Claims 2-4, 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Hallgren et al. (Biochemistry 39:13068-13077, 2000).

Claims 2-4 are directed in part to a polynucleotide encoding a fusion protein wherein said fusion protein comprises (1) mouse mast cell protease 6, and (2) a label polypeptide. Claim 7 is directed in part to a cell comprising a polynucleotide encoding a fusion protein, wherein the fusion protein comprises (1) a mouse mast cell protease 6, and (2) a label polypeptide.

Hallgren et al. teach the cloning and expression of a fusion protein comprising mouse mast cell protease 6 and a 6xHis tag (Abstract). Hallgren et al. teach a vector comprising a polynucleotide encoding the fusion protein (page 13069, left column, pCEP-Pu2 vector) and cells comprising said vector (page 13069, right column, Transfection of 293-EBNA cells). Thus, the polynucleotide and cells of Hallgren et al. anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Benfey et al. (J. Biol. Chem. 262(11):5377-5384, 1987) in view of Hallgren et al. (Biochemistry 39:13068-13077, 2000). Benfey et al. teach cloning of the rat mast cell protease II (RMCP II), the nucleotide sequence of the RMCP II cDNA, and the amino acid sequence of RMCP II (Abstract; Figure 1). Benfey et al. do not teach a fusion protein comprising the RMCP II protein and a label polypeptide. The teachings of Hallgren have been discussed above. Hallgren et al. do not teach a fusion protein comprising RMCP II.

Claim 5 is directed in part to a nucleic acid encoding a fusion protein, wherein said fusion protein comprises RMCP II and a label polypeptide. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further add a polynucleotide encoding a 6xHis tag to the polynucleotide of Benfey et al. such that the resulting polynucleotide would encode a RMCP II-6xHis fusion protein. A person of ordinary skill in the art is motivated to construct such a polynucleotide for the benefit of obtaining a polypeptide which can be easily purified. Substantial amounts of purified RMCP II are desirable for further functional characterization as this protein is one of the proteases found in secretory granules of mast cells. One of ordinary skill in the art has a reasonable expectation of success at constructing such polynucleotide since Hallgren et al. teach a similar polynucleotide with a different mast cell protease, and also in view of the

fact that construction of polynucleotides which encode 6xHis fusion proteins is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

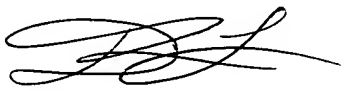
Conclusion

20. No claim is in condition for allowance.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



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DR
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